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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/466,935	12/20/1999	VITALIY ARKADYEVICH LIVSHITS	0010-1070-0	1750

38108 7590 05/04/2004

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EXAMINER	
STEADMAN, DAVID J	

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 05/04/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/466,935	LIVSHITS ET AL.	
	Examiner	Art Unit	
	David J Steadman	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 February 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *16,17 and 37-63* is/are pending in the application.

4a) Of the above claim(s) *49-63* is/are withdrawn from consideration.

5)☒ Claim(s) *16* is/are allowed.

6)☒ Claim(s) *17 and 37-48* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

[1] In view of the appeal brief filed on February 25, 2004, PROSECUTION IS HEREBY REOPENED. A new ground of rejection is set forth below.

To avoid abandonment of the application, appellant must exercise one of the following two options:

(1) file a reply under 37 CFR 1.111 (if this Office action is non-final) or a reply under 37 CFR 1.113 (if this Office action is final); or,

(2) request reinstatement of the appeal.

If reinstatement of the appeal is requested, such request must be accompanied by a supplemental appeal brief, but no new amendments, affidavits (37 CFR 1.130, 1.131 or 1.132) or other evidence are permitted. See 37 CFR 1.193(b)(2).

[2] Claims 16-17 and 37-63 are pending in the application.

[3] The text of those sections of Title 35 U.S. Code not included in the instant action can be found in a prior Office action.

Claims Rejections – 35 USC 112, Second Paragraph

[4] Claims 17 and 37-48 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

[a] Claims 17 and 37 (claims 38-39, dependent therefrom) 40-42, 43 (claims 44-45 dependent therefrom), and 46-48 are indefinite in the recitation of "an activity of making a bacterium having the protein L-threonine resistant," "an activity of a protein which

makes the bacterium harboring the protein L-threonine resistant," or "an activity of a protein which makes the bacterium harboring the protein L-homoserine resistant." It is unclear from the claims and the specification as filed as to the "activity" which imparts L-threonine or L-homoserine resistance to a protein. Furthermore, it is unclear as to the meaning of the term "L-threonine resistant" and "L-homoserine resistant." It is suggested that appellants clarify the meaning of the terms.

[b] Claims 38-39 and 44-45 are indefinite in the recitation of "an activity of the protein." It is unclear from the claims as to whether the term refers to the activity which makes the protein L-threonine or L-homoserine resistant or some other activity. It is suggested that appellants clarify the meaning of the term.

[c] Claims 39, 42, 45, and 48 are unclear in the recitation of "functions efficiently." It is unclear as to how one is to distinguish between a promoter that "functions efficiently" and a promoter that functions inefficiently. It is suggested that appellants clarify the meaning of the claims.

Claims Rejections – 35 USC 112, First Paragraph

[5] Claims 17 and 37-48 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 17 and 43 recite (in relevant part) a genus of isolated DNAs that hybridize to nucleotides 187-804 of SEQ ID NO:3 under a recited stringent condition and encode a protein having an activity of making a bacterium having the protein L-threonine resistant. Claims 37-48 are drawn to a genus of modified Escherichia coli bacteria having increased expression of SEQ ID NO:4 and optionally SEQ ID NO:2 by increasing expression of SEQ ID NO:2 or 4-encoding DNA by any method, optionally wherein the modification is to increase DNA copy number by any method or the modification is to substitute the "promoter sequence of the gene coding for the protein" with any nucleic acid that promotes DNA expression.

For claims drawn to a genus, MPEP § 2163 states the written description requirement for a genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. See Eli Lilly, 119 F.3d at 1568, 43 USPQ2d at 1406. MPEP § 2163 states that a representative number of species means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. In this case, the genus encompasses widely

variant species. The genus of nucleic acids as recited in claims 17 and 43 encompasses species having widely variant structures, i.e., all nucleic acids that hybridize under the recited conditions to nucleotides 187-804 of SEQ ID NO:3, and widely variant functions, i.e., any "activity of making a bacterium having the protein L-threonine resistant" and the genus of E. coli bacteria of claims 37-48 encompasses widely variant species with respect to the modifications which achieve the desired result of increased DNA expression, increased copy number, or promoter substitution. In this case, the specification discloses only a single representative species of the recited DNA of claims 17 and 43, i.e., SEQ ID NO:3, and only two representative species of the claimed modified E. coli bacteria of claims 37-48, i.e., a bacterial host cell comprising an expression vector, wherein the expression vector has a nucleic acid encoding the polypeptide of SEQ ID NO:2 or 4. These representative species fail to represent the entire genus of species as encompassed by the claims. Given the lack of description of a representative number of DNAs and modified E. coli bacteria, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicant was in possession of the claimed invention.

[6] Response to arguments: Appellants argue (beginning at page 6 of the appeal brief) the genus of modified E. coli bacteria is a small genus and that the examiner fails to understand the limitations of the claims and the scope of the genus. Appellants argue that the examiner's interpretation of the scope of the claimed genus "is simply wrong, misstates the literal scope of the claims, and evinces a deep misunderstanding of the

claimed subject matter." Appellants further argue: 1) the claims are not limited to any protein that makes the bacteria L-threonine resistant or L-homoserine resistant, but to SEQ ID NO:4 or SEQ ID NO2, respectively, which is a single species of protein; 2) the skilled artisan must only determine those promoters that result in increased expression of DNA encoding SEQ ID NO:4 or SEQ ID NO:2, which is routine; and 3) the skilled artisan must select a multicopy vector to use for expression of the DNA that encodes SEQ ID NO:4 or SEQ ID NO:2, which is routine. Appellants argue increasing protein activity by increasing DNA expression can be accomplished by methods allegedly well-known in the art and allegedly described in the specification. Appellants' remaining remarks attempt to define the species encompassed by the claimed genus. Appellants' argument is not found persuasive.

Contrary to appellants' argument, the examiner has properly interpreted the species encompassed by the claimed genus of nucleic acids and modified bacteria in accordance with MPEP 2111, which directs the examiner to give claims their broadest reasonable interpretation. Moreover, the examiner fully understands the species encompassed by the genus of claimed nucleic acids and modified bacteria. In this case, the claimed genus is not "very small", but is instead a broad genus that encompasses widely variant species that have not been described in the specification. Addressing argument 1), the examiner acknowledges that the genus of DNAs "coding for the protein" as recited in claims 37-42 and 44-48 is limited to those encoding SEQ ID NO:2 or 4. However, it is not the genus of DNAs encoding SEQ ID NO:2 or 4 of claims 37-48 that is at issue. Instead, it is the genus of claimed E. coli bacteria, which has any

modification(s) that results in increased expression of DNA coding of SEQ ID NO:2 or 4 (claims 37, 40, 43, and 46), any modification(s) that results in an increase in copy number of the DNA coding for SEQ ID NO:2 or 4 (claims 38, 41, 44, and 47), or substitution of "a promoter sequence of the gene coding for" the protein of SEQ ID NO:2 or 4 with any nucleic acid sequence that promotes DNA expression and "functions efficiently" (claims 39, 42, 45, and 48). It should be noted that the genus of DNAs as recited in claims 17 and 43 is not limited to encoding SEQ ID NO:4 and instead encompasses species that are widely variant with respect to their structures and functions (as described above). Addressing argument 2) it is noted that appellants' argument appears to address the scope of enablement rejection and not the instant written description rejection. Nonetheless, it is noted that the specification fails to identify which – if any – of the nucleotides of SEQ ID NO:1 and 3 are considered to be the promoter such that one of skill can substitute the promoter of the gene encoding SEQ ID NO:2 or 4 with a nucleic acid that has the ability to promote DNA expression. Further, the nucleic acid that promotes DNA expression that is used as a substitute is not limited to those of the prior art, but encompasses any nucleotide sequence that promotes increased DNA expression. While the function of the genus of nucleic acids that promote DNA expression that is used as a substitute may be described, their structures clearly are not and there is no common structural feature(s) that are possessed by members of the genus such that a skilled artisan can visualize all members of the genus. Addressing argument 3), while the use of a multicopy vector for increased DNA expression is known in the prior art, this argument is not commensurate

in scope with the claims. In this case, increased DNA expression, optionally by increasing DNA copy number, can be achieved by any modification to the bacterium – the modification is not limited to the use of a multicopy vector. There is no dispute that multicopy vectors for increased DNA expression are known in the art. Nor is there any dispute that the substitution of a known chromosomal promoter sequence with another promoter for increased DNA expression is known in the art. However, the claimed genus of modified E. coli bacteria is not so limited to the use of multicopy vectors or to substitution of the gene's promoter (whatever the sequence of that promoter may be as it is not described or identified) with an art recognized nucleic acid that promotes DNA expression. For these reasons and the reasons stated in item [5] above, the claimed genus of DNAs and modified E. coli bacteria encompass species that are widely variant and the two representative species of modified E. coli bacteria as cited above fail to represent the entire genus.

[7] Claims 17 and 37-48 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated nucleic acid encoding the polypeptide of SEQ ID NO:2 or 4 and a host cell comprising an expression vector, wherein the expression vector comprises said isolated nucleic acid, does not reasonably provide enablement for all DNAs as recited in claims 17 and 43 and all modified bacteria as encompassed by claims 37-48. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

It is the examiner's position that undue experimentation would be required for a skilled artisan to make and/or use the entire scope of the claimed invention. Factors to be considered in determining whether undue experimentation is required are summarized in *In re Wands* (858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)) as follows: (A) The breadth of the claims; (B) The nature of the invention; (C) The state of the prior art; (D) The level of one of ordinary skill; (E) The level of predictability in the art; (F) The amount of direction provided by the inventor; (G) The existence of working examples; and (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure. See MPEP § 2164.01(a). The Factors most relevant to the instant rejection are addressed in detail below.

- The claims are overly broad in scope: Claims 17 and 43 are so broad as to encompass any DNA that hybridizes under the recited conditions to nucleotides 187-804 having the desired activity. Claims 37-48 are so broad as to encompass an E. coli bacterium having increased expression of SEQ ID NO:4 and optionally SEQ ID NO:2 by increasing copy number by any method, optionally wherein the modification is to increase copy number by any method or the modification is to substitute the promoter with any promoter, including those promoters that are known and those that have yet to be isolated. The broad scope of claimed polynucleotides is NOT commensurate with the enablement provided by the disclosure with regard to the extremely large number of DNAs encompassed by claims 17 and 43 and modified bacteria as encompassed by claims 37-48. In this case the disclosure is limited to an isolated nucleic acid encoding

the polypeptide of SEQ ID NO:2 or 4 and a host cell comprising an expression vector, wherein the expression vector comprises said isolated nucleic acid.

- The lack of guidance and working examples: The specification provides only two working examples of the recited DNA, i.e., SEQ ID NO:1 and 3 and provides only two working examples of modified E. coli bacteria, i.e., E. coli transformed with expression vectors comprising SEQ ID NO:1 and 3. While the specification provides additional non-specific guidance for making other DNAs and modified E. coli host cells, the specification fails to provide the necessary specific guidance for making the full scope of recited DNAs and modified E. coli bacterium. Regarding the recited DNAs, the specification fails to provide guidance regarding those nucleotides of SEQ ID NO:3 that may be altered by substitution, addition, insertion, and/or deletion with an expectation of maintaining the desired activity. Regarding the recited modified E. coli bacterium, the specification fails to provide guidance regarding those modifications – even for those claims that limit the modifications to increasing copy number or promoter substitution. It should be noted that the specification fails to identify those nucleotides of SEQ ID NO:1 and 3 – if any –that are considered to be the respective gene promoter sequence.

- The high level of unpredictability in the art: There is a high level of unpredictability in altering the nucleotide sequence of an encoding nucleic acid or altering a bacterium by any means with an expectation of obtaining a nucleic acid or bacterium having the desired characteristic(s). Regarding an encoding nucleic acid, the sequence of a nucleic acid determines the corresponding encoded protein's structural and functional properties. Predictability of which changes can be tolerated in an

encoded protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e., expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. The positions within an encoding nucleic acid's sequence where modifications can be made with a reasonable expectation of success in obtaining an encoded polypeptide having the desired activity/utility are limited in any protein and the result of such modifications is highly unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g., multiple substitutions. Similarly, an E. coli bacterium comprises numerous encoding nucleic acids, thus, the effects of altering the genotype of an E. coli bacterium with an expectation of obtaining the desired phenotype is even more complex.

- The state of the prior art supports the high level of unpredictability: The state of the art provides evidence for the high level of unpredictability in altering a polynucleotide sequence with an expectation that the encoded polypeptide will maintain the desired activity/utility. For example, Branden et al. ("Introduction to Protein Structure", Garland Publishing Inc., New York, 1991) teach "[p]rotein engineers frequently have been surprised by the range of effects caused by single mutations that they hoped would change only one specific and simple property in enzymes" and "[t]he often surprising results of such experiments reveal how little we know about the rules of protein stability... ...they also serve to emphasize how difficult it is to design *de novo* stable

proteins with specific functions" (page 247). While it is acknowledged that this reference was published in 1991, to date there remains no certain method for reasonably predicting the effects of even a *single* amino acid mutation on a protein. Thus, the prior art acknowledges the unpredictability of altering a protein-encoding sequence with an expectation of obtaining a protein having a desired function and discloses that even a single substitution in a polypeptide's amino acid sequence may completely alter the function of a polypeptide. As stated above, as an E. coli bacterium comprises numerous encoding nucleic acids and thus one would expect the effects of altering an E. coli bacterium with an expectation of obtaining the desired effect is significantly more unpredictable.

- The amount of experimentation required is undue: While methods of generating variants of a given polynucleotide and a given bacterium are known, e.g., by mutagenesis, it is not routine in the art to screen for all polynucleotides and modified E. coli bacteria having a substantial number of modifications as encompassed by the instant claims. Thus, in view of the overly broad scope of the claims, the lack of guidance and working examples provided in the specification, and the high degree of unpredictability as evidenced by the prior art, undue experimentation would be necessary for a skilled artisan to make and use the entire scope of the claimed invention.

As such, appellants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims. The scope of the claims must bear a reasonable

correlation with the scope of enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

[8] Response to arguments: Appellants argue (beginning at page 9 of the appeal brief) the examiner has not interpreted the claims correctly and the analysis of the Factors of In re Wands in the Office action mailed March 25, 2003 is moot as the claims have been amended following that Office action. Specifically, appellants argue the claims are not so limited to modified E. coli bacterium having increased expression of a protein, but to increased expression of a specific protein. Appellants argue the increase in protein activity is accomplished via increased DNA expression, which is accomplished by increasing copy number of the encoding DNA or by promoter substitution of the corresponding gene's promoter in the bacterial chromosome, allegedly acknowledged by the examiner as being well-known methods in the art. Appellants argue that the examiner has read the claims to be much broader than their meaning allows. Appellants argue that a skilled artisan can make the full scope of the claimed invention based on the disclosure and the state of the art at the time of the invention. Appellants' argument is not found persuasive.

Contrary to appellants' argument, the examiner has properly interpreted the scope of the claims in accordance with MPEP 2111, which directs the examiner to give claims their broadest reasonable interpretation. Moreover, the examiner fully

understands the scope of claimed subject matter. The increase in the expression of DNA encoding SEQ ID NO:4 and optionally SEQ ID NO:2 of the bacterium of claims 37, 40, 43, and 46 is accomplished by any method, while claims 38-39, 41-42, 44-45, and 47-48 limit the modification to increasing a copy number of the DNA by any method or substitution of the corresponding gene's promoter (whatever sequence it may have as the specification fails to identify the promoter of the gene encoding SEQ ID NO:2 or 4) with any other nucleic acid that promotes DNA expression, including those that have yet to be isolated. While methods of increasing DNA copy number of a given encoding nucleic acid are known, e.g., by inserting the nucleic acid into a high copy number vector, and methods of promoter substitution are known using art recognized nucleic acids that promote DNA expression, the claims are not limited to increasing DNA copy number by inserting the nucleic acid into a high copy number vector or substitution using nucleic acids that promote DNA expression that are known in the prior art. For these reasons and the reasons stated in item [7] above, the claims are not commensurate in scope with the enablement provided by the specification.

Conclusion

[9] Status of the claims:

- Claims 16-17 and 37-63 are pending in the application.
- Claims 17 and 37-48 are rejected.
- Claims 49-63 are withdrawn from consideration.
- Claim 16 is in condition for allowance.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Steadman, whose telephone number is (571) 272-0942. The Examiner can normally be reached Monday-Friday from 7:00 am to 5:00 pm. If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Ponnathapura Achutamurthy, can be reached at (571) 272-0928. The FAX number for submission of official papers to Group 1600 is (703) 308-4242. Draft or informal FAX communications should be directed to (571) 273-0942. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Art Unit receptionist whose telephone number is (703) 308-0196.

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Art Unit 1652
04-30-04

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